NL67388.041.20 - CATERPILLAR

CATERPILLAR STUDY

DMC CHARTER CATERPILLAR-Study

1. INTRODUCTION	
Name, sponsor's ID and EUDRACT number	The efficacy of a lock solution containing taurolidine, citrate and heparin for the prevention of tunneled central line-associated bloodstream infections in pediatric oncology patients, a randomized controlled, mono-centre trial (CATERPILLAR-study) Sponsor's ID: NL67388.041.20
Objectives of trial	Investigator-initiated, mono-center, open-labelled randomized controlled trial to compare the efficacy of the taurolidine-citrate-heparin lock and the heparin lock in the prevention of tunnelled central line associated bloodstream infections in pediatric oncology patients. Patients in the intervention study arm will receive lock solutions containing taurolidine 1.35%, citrate 4.0%, and heparin 100 IU/ml. Patients in the control study arm will receive lock solutions containing heparin 100 IU/ml. The lock solutions will be instilled with a maximum of once weekly, and a minimum of once every three weeks.
Scope of the charter	The purpose of this document is to describe the roles and responsibilities of the independent DMC for the CATERPILLAR trial, including the timing of meetings, methods of providing information to and from the DMC, frequency and format of meetings, statistical rules and relationships with other committees.
2. ROLES AND RESPONSIBILITIES	
The aims of the committee	To safeguard the interests of trial participants, assess the safety and efficacy of the interventions during the trial, and monitor the overall conduct of the clinical trial.
Terms of reference	The DMC should receive and review the progress and accruing data of this trial and provide advice on the conduct of the trial to the Trial Steering Committee. The DMC should inform the Chair of the steering committee if, in their view: ○ The results are likely to convince a broad range of clinicians, including those supporting the trial and the general clinical community, that one trial arm is clearly indicated or contraindicated, and there was a reasonable expectation that this new evidence would materially influence patient management; **or** ○ It becomes evident that no clear outcome would be obtained.
Specific roles of the DMC	○ Interim review of the trial's progress including updated figures on recruitment, data quality, and main outcomes and safety data. ○ Assess data quality, including completeness ○ Monitor recruitment figures and losses to follow-up ○ Monitor compliance with the protocol by participants and investigators ○ Monitor trial conduct – organisation and implementation of trial protocol ○ Monitoring evidence for treatment differences in the main efficacy outcome measures ○ Monitor evidence for treatment harm (eg toxicity data, SAEs, deaths) ○ Decide whether to recommend that the trial continues to recruit participants or whether recruitment should be terminated either for everyone or for some treatment groups and/or some participant subgroups ○ Suggest additional data analyses ○ Advise on protocol modifications suggested by investigators or sponsors (eg to inclusion criteria, trial endpoints, or sample size) ○ Monitor planned sample size assumptions ○ Monitor continuing appropriateness of patient information ○ Assess the impact and relevance of external evidence

NL67388.041.20 - CATERPILLAR

3. BEFORE OR EARLY IN THE TRIAL	
Input into the protocol by the DMC	All potential DMC members should have sight of the protocol/outline before agreeing to join the committee. Before recruitment begins the trial will have undergone review by the clinical research committee (CRC) of the Princess Maxima Center and the research ethics committee (METC) of the University Medical Center Utrecht. Therefore, if a potential DMC member has major reservations about the trial (e.g. the protocol or the logistics) they should report these to the trial office and may decide not to accept the invitation to join. DMC members should be independent and constructively critical of the ongoing trial, but also supportive of aims and methods of the trial.
Start of the trial meeting	A teleconference call will be held with the DMC members before the trial starts or early in the course of the trial, to discuss the protocol, trial, analysis plan, future meetings, and to have the opportunity to clarify any aspects with the principal investigators. An initial "dummy" report will be given to the DMC to familiarise the DMC members with the format that will be used in the reports.
DMC member registration	DMC members will formally register their assent by confirming (1) that they agree to be on the DMC and (2) that they agree with the contents of this Charter.
4. Composition	
Membership and size of the DMC	The members of the DMC for this trial are: 1. Dr. Marieke Witvliet, Pediatric Surgeon, Wilhelmina Children's Hospital, Utrecht, the Netherlands. 2. Dr. Bart Rijnders, Infectious Diseases, Erasmus Medical Center, Rotterdam, the Netherlands. 3. Prof Dr. Hein Putter, Medical Statistician, Leids University Medical Center, Leiden, the Nethterlands.
The Chair, how they are chosen and the Chair's role.	The Chair was chosen by the sponsor. The Chair will be: dr. Marieke Witvliet. The Chair is expected to facilitate and summarise discussions.
The responsibilities of the DMC statistician	The DMC membership will include a statistician to provide independent statistical expertise.
The responsibilities of the trial statistician	The trial statistician will produce (or oversee the production of) the report to the DMC, and may participate in the first part of the DMC meetings to explain how the statistical analysis has been performed.
The responsibilities of the trial office team	The trial office team (e.g. trial Manager, data-management etc.) only inputs to the production of the non-confidential sections of the DMC report.
The responsibilities of the PI and other members of the Trial Management Group (TMG)	The PI, may be asked, and should be available, to attend open sessions of the DMC meeting. The other TMG members will not usually be expected to attend but can attend open sessions of the DMC when necessary.
5. Relationships	
Relationships	The sponsor is the Princess Maxima Center. The Principal Investigator (Prof. Dr. M.H.W.A. Wijnen) is the head of the Department of Pediatric Surgery of the Princess Maxima Center for pediatric oncology. The Trial Steering Committee consists of: ○ Prof. Dr. M.H.W.A. Wijnen, Pediatric Surgeon, Princess Maxima Center. ○ Dr. M.D. van de Wetering, Pediatric Oncologist, Princess Maxima Center. ○ Dr. C.P. van de Ven, Pediatric Surgeon, Princess Maxima Center. ○ Prof. Dr. M. Zwaan, Pediatric Oncologist, Head of the Trial Office, Princess Maxima Center. The trial office team consists of: ○ Prof. Dr. M. Zwaan, Pediatric Oncologist, Head of the Trial Office, Princess Maxima Center. ○ MSc Anne Elsinghorst, Trial Manager, Princess Maxima Center. ○ Jan Lieverst, Trial Office, Princess Maxima Center.

	○ Inekee van der Vaart, Trial Office, Princess Maxima Center. ○ Associate Prof. Dr. M. Fiocco, Statistician, Princess Maxima Center. ○ Drs. C.H. van den Bosch, PhD-student, Princess Maxima Center.
Decisions of the DMC	The DMC does not make decisions about the trial but makes recommendations to the Trial Steering Committee and its Chair (Prof. Dr. M.H.W.A. Wijnen).
Payments to DMC members	The meetings will be held by teleconference. If a face-to-face meeting will be held, members will be reimbursed for travel expenses.
The need for DMC members to disclose information about any competing interests	The DMC members will declare any conflicts of interests using the competing interests form (annex 2). These forms will be stored at the Trial Office of the Princess Maxima Center.
6. ORGANISATION OF DMC MEETINGS	
Expected frequency of DMC meetings	The DMC will meet prior to the start of the study and after the inclusion of 231 patients, approximately one year after the start of the study. Before the DMC meeting, the interim analyses should be performed. At the end of the study, another DMC meeting will be organised.
Whether meetings will be face-to-face or by teleconference	The meetings will be held by teleconference.
How DMC meetings will be organised, especially regarding open and closed sessions, including who will be present in each session	Only DMC members and others whom they specifically invite, e.g. the trial statistician, are present in closed sessions. In the session prior to the start of the study and at the end of the study, all those attending the closed session are joined by the PI (Prof. Dr. M.H.W.A. Wijnen), and/or the head of the trial** office (Prof. Dr. Michel Zwaan). 1. Start of the study session. 2. Closed session will be performed after the inclusion of 231patients (50%): DMC discussion of “closed” parts of the report. 3. End of the study session.
7. TRIAL DOCUMENTATION AND PROCEDURES TO ENSURE CONFIDENTIALITY AND PROPER COMMUNICATION	
Intended content of material to be available in closed sessions	Accumulating information relating to recruitment and data quality will be presented. The interim analysis will be performed based on the primary outcome measure (central-line associated bloodstream infections) and the stopping rule will be evaluated. The results of the interim analysis will be presented during the meeting. Additionally, safety data will be compared between the two treatment groups and presented (e.g. toxicity details in terms of known of serious adverse events).
Will the DMC be blinded to the treatment allocation	The DMC will not be blinded.
Who will see the accumulating data and interim analysis	The DMC members will see the accumulating data and interim analysis. DMC members do not have the right to share confidential information with anyone outside the DMC, including the PI.
Who will be responsible for identifying and circulating external evidence (eg from other trials/ systematic reviews)	Identification and circulation of external evidence (e.g. from other trials/ systematic reviews) is not the responsibility of the DMC members. The trials office team will collate such information.
To whom the DMC will communicate the decisions/ recommendations that are reached	The DMC usually will report its recommendations writing a document for the Trial Steering Committee. This should be copied to the trial statistician and trial manager and if possible should be sent via the trials office in time for consideration at a TSC meeting.
Whether reports to the DMC be available before the meeting or only at/during the meeting	The DMC will receive the report at least 2 weeks before any meetings.

What will happen to the confidential papers after the meeting	The DMC members should store the papers safely after the meeting. After the trial is reported, the DMC members should destroy all interim reports.
8. DECISION MAKING	
What decisions/recommendations will be open to the DMC	Possible recommendations could include: ○ No action needed, trial continues as planned ○ Early stopping due, for example, to clear benefit or harm of a treatment, futility, or external evidence ○ Stopping recruitment within a subgroup ○ Extending recruitment (based on actual control arm response rates being different to predicted rather than on emerging differences) or extending follow-up ○ Stopping a single arm of a multi-arm trial ○ Sanctioning and/or proposing protocol changes
Statistical methods	<u>Primary analysis</u> The primary end-point is the incidence of CLABSIs. The percentage of first tunnelled CLABSI in each group will be reported. To test the equality of the two proportions a Binomial test will be used. <u>Stopping rule</u> This method described below will be used as a rule, not as a guideline. After inclusion of the first 231 patients an interim analysis will be performed by the trial statistician. The results will be presented at the second DMC meeting, see chapter 9.4. The stopping rule is based on testing the one-sided test at $\alpha = 0.025$ for H0: 'experimental incidence ≥ control incidence' against H1: 'experimental incidence < control incidence'. The test is one-sided because there is no need to prove superiority of the control treatment in case it is better than the experimental. The stopping rule allows stopping for acceptance of the alternative hypothesis (superiority) as well as stopping for acceptance of the null hypothesis (futility). The stopping boundaries are based on choices of the α- and β-spending functions. The α-spending function determines how eager or reluctant one is to stop the trial for superiority. The β-spending function determines how eager or reluctant one is to stop the trial because the chance has become small that superiority can be concluded if the trial is continued. As α-spending function we have chosen the Jennison and Turnbull power family function with $\rho = 2.35$. This choice implies that the trial is stopped after 200 patients if the one-sided P-value is smaller than 0.005 (or 0.01 two-sided) in favor of the experimental treatment. As β-spending function we have chosen the Jennison and Turnbull power family function with $\rho = 3.2$. This choice implies stopping the trial after 231 patients if the one-sided P-value is ≥ 0.5, i.e. if the estimated treatment effect at that time is in favor of the control treatment. <u>Safety analysis</u> Percentages of serious adverse events will be reported for both treatment groups.
How decisions or recommendations will be reached within the DMC	It is recommended that every effort should be made by the DMC to reach a unanimous decision. If the DMC cannot achieve this, a vote may be taken, although details of the vote should not be routinely included in the report to the TSC as these may inappropriately convey information about the state of the trial data. It is important that the implications (e.g. ethical, statistical, practical, financial) for the trial are considered before any recommendation is made.
When the DMC is quorate for decision-making	Effort should be made for all members to attend. The trial office team will try to ensure that a date is chosen to enable this. Members who cannot attend the meeting should be encouraged to attend by teleconference. If, at short notice, any DMC members cannot attend at all then the DMC may still meet if at least one statistician and one clinician, including the Chair (unless otherwise agreed), will be present. If the DMC is considering recommending major action after such a meeting the DMC Chair should talk with the absent members as

	soon after the meeting as possible to check they agree. If they do not, a further teleconference should be arranged with the all DMC members.
Input of DMC members who cannot attend	If the report is circulated before the meeting, DMC members who will not be able to attend the meeting may write comments to the DMC Chair to be used during the discussions.
What happens to members who do not attend meetings	If a member does not attend a meeting, he should attend the next meeting. In case of repeated absence he should be replaced.
Whether different weight will be given to different endpoints (eg safety/efficacy)	A different weight will not be given to the different end-points.
9. REPORTING	
To whom will the DMC report their recommendations/decisions, and in what form	A letter to the head of the Trial Steering Committee (Prof. Dr. M.H.W.A. Wijnen) will be written by the DMC within 3 weeks (format annex 3). A copy of this letter will be lodged with the trial office. This should be copied to the trial statistician and trial manager and if possible should be sent via the trials office in time for consideration at a TSC meeting.
Whether minutes of the meeting be made and, if so, by whom and where they will be kept	Minutes of the meeting will be made by one of the DMC members, these minutes will be kept at the trial office of the Princess Maxima Center.
What will be done if there is disagreement between the DMC and the body to which it reports	In case of disagreement, a meeting between the groups should be held. It will depend on the reason for the disagreement what information will be presented. The meeting should be chaired by a senior member of the trials office staff or an external expert who is not directly involved with the trial.
10. AFTER THE TRIAL	
Publication of results	At the end of the trial there will be a meeting to allow the DMC to discuss the final data analysis with principal trial investigator. The DMC may wish to see a statement that the trial results will be published in a correct and timely manner.
The information about the DMC that will be included in published trial reports	DMC members will be named and their affiliations listed in the main report, unless they explicitly request otherwise. A short summary about DMC meetings should be reported.
Whether the DMC will have the opportunity to approve publications, especially with respect to reporting of any DMC recommendation regarding termination of a trial	The DMC may wish to be given the opportunity to read and comment on any publications before submission.
Any constraints on DMC members divulging information about their deliberations after the trial has been published	The DMC may discuss issues from their involvement in the trial 12 months after the primary trial results have been published, or when permission is agreed with the overseeing committee.

NL67388.041.20 - CATERPILLAR

Annex 1: List of abbreviations

DMC	Data Monitoring Committee
SAE	Serious Adverse Events
PI	Principal Investigator
TMG	Trial Management Group
TSG	Trial Steering Committee

NL67388.041.20 - CATERPILLAR

Annex 2: Competing interests form

Potential competing interests of Data Monitoring Committee members for *the CATERPILLAR-study (*NL67388.041.20)

The avoidance of any perception that members of a DMC may be biased in some fashion is important for the credibility of the decisions made by the DMC and for the integrity of the trial.

Possible competing interest should be disclosed via the trials office. In many cases simple disclosure up front should be sufficient. Otherwise, the (potential) DMC member should remove the conflict or stop participating in the DMC. Table 1 lists potential competing interests.

Table 1: Potential competing interests

- Stock ownership in any commercial companies involved
- Stock transaction in any commercial company involved (if previously holding stock)
- Consulting arrangements with the sponsor
- Frequent speaking engagements on behalf of the intervention
- Career tied up in a product or technique assessed by trial
- Hands-on participation in the trial
- Involvement in the running of the trial
- Emotional involvement in the trial
- Intellectual conflict eg strong prior belief in the trial's experimental arm
- Involvement in regulatory issues relevant to the trial procedures
- Investment (financial or intellectual) in competing products
- Involvement in the publication

Please complete the following section and return to the Trial Office of the Princess Maxima Center.

☐ **No,** I have no competing interests to declare
☐ **Yes,** I have competing interests to declare (please detail below)

Please provide details of any competing interests: _____

_____

_____

Name: _____

Signed: _____ Date: _____

NL67388.041.20 - CATERPILLAR

Annex 3: Suggested report from DMC to TSC where no recommendations are being made

[Insert date]

To: Chair of Trial Steering Committee

Dear Prof. Dr. M.H.W.A. Wijnen

The Data Monitoring Committee (DMC) for the CATERPILLAR trial met on *[meeting date]* to review its progress and interim accumulating data. *[List members] attended* the meeting and reviewed the report.

We congratulate the trial organisers and collaborators on the progress and conduct of the trial and the presentation of the data. The trial question remains important and, on the basis of the data reviewed at this stage, we recommend continuation of the trial according to the current version of the protocol *[specify protocol version number and date]* with no changes.

We shall next review the progress and data *[provide approximate timing]*

Yours sincerely,

[Name of meeting Chair]
Chair of Data Monitoring Committee

On behalf of the DMC (all members listed below)

DMC members:
(1) [*Insert name and role*]
(2) [*Insert name and role*]
(3) [*Insert name and role*]